Cystic Fibrosis why we're here

How our research makes a difference:
Research Impact Report 2013–2021

Fighting for a Life Unlimited

Contents

Foreword

To me, research into cystic fibrosis (CF) is about achieving the best life for my children and others living with the condition. I've been lucky to be involved in work that the Trust does behind the scenes around research, including identifying the top 10 priorities for clinical research in CF through the James Lind Alliance Priority Setting Partnership. I have witnessed incredible work and met some inspiring people, all working towards the goal of a 'life unlimited' from the challenges of cystic fibrosis.

I passionately believe in people with lived experiences driving forward research, and the CF community have been an incredibly loud and powerful voice in establishing what the research priorities should be. I'm delighted to see throughout this report that the Trust is funding research towards answering these priorities: answers which will create tangible, day-to-day differences, not just for people with the condition, but for their loved ones and their families in years to come.

Thanks to research, the world is looking so much brighter for people with cystic fibrosis. There have been so many advances in the time since my children were diagnosed; however, now is not the time to rest on our laurels. We need to harness the energy across the community and really push forward with supporting future research. This way we can make life with CF the best it can be.

Zoë Elliott

Introduction

Welcome to the Cystic Fibrosis Trust's first Research Impact Report. It covers the achievements we have made in moving towards new treatments for CF since the publication of our first research strategy in 2013. In that time we've invested £18.4 million in 91 research grants, supporting 138 researchers to work in CF research. The scope and ambition of the research programme has been guided by the health priorities identified by the CF community through the James Lind Alliance Priority Setting Partnership[1] and covers a huge range of topics including basic biomedical research, the UK CF Innovation Hub and the CF Syndicate in Antimicrobial Resistance (AMR). It runs from inspiring undergraduate biomedical students to pursue a career in CF research within our Summer Studentship scheme, to attracting world-leading professors to apply their skills and expertise to tackle specific issues in CF research.

Over the last eight years, research we have funded has resulted in over 200 publications to date. Each represents the sharing of new knowledge with the rest of the CF research community. Every publication is the result of years of work, and moves us a step closer to improving and extending the lives of people with cystic fibrosis. Examples highlighted in this report include findings that called for a new direction for research into CF-related diabetes (CFRD), hope for increasing the effectiveness of existing antibiotics against *Pseudomonas aeruginosa* infection, and important advances in methodology to better test the effects of new CF drugs in the lab.

Advances such as these have only been possible through collaborative and multidisciplinary team working, where each member of the team brings unique knowledge and perspective. An important principle of the way that we fund research is to encourage researchers to build and foster collaboration. Each of our multi-year Strategic Research Centre (SRC) grants typically involve eight principal investigators, working in four different cities in three countries around the world. Collaboration with a wide range of partners, from universities to biotech and biopharmaceutical companies, is further promoted through our Venture and Innovation Awards (VIAs), which provide leverage for additional funding to support exciting research opportunities. From a Trust investment of £4.1 million through this VIA scheme alone, we have leveraged an additional £17.7 million since 2013.

Building strategic partnerships with other research funders is increasingly important to the Trust as it allows us to add value to our investments in research. For example, co-investment with the University of Cambridge, and the leverage of these funds, has brought together a truly world-leading collaboration of exceptional calibre to form the UK CF Innovation Hub. The aim of the UK CF Innovation Hub is to harness multidisciplinary world-class research to accelerate progress towards preventing lung damage in CF and subsequent loss of lung function. The researchers are tackling ambitious and innovative 'high stakes' programmes of work and are making good progress. In this report, we highlight their use of a novel 'fragment-based drug design' (FBDD) approach for the first time in antimicrobial drug discovery to develop new drugs for the CF lung infection *Mycobacterium abscessus*.


Dr Lucy Allen

While a long-term aim of the Trust is to tackle the underlying cause of CF and develop future treatments, we also continue programmes to pursue research that will improve the health and wellbeing of people living with CF today. For example, in 2016 a Trust-funded investigation into the transmission of *M. abscessus* found for the first time that infection can be passed from person to person, which quickly led to the introduction of new cross-infection guidelines and informed the design of a more rigorous air conditioning system for the CF clinic in the new Royal Papworth Hospital.

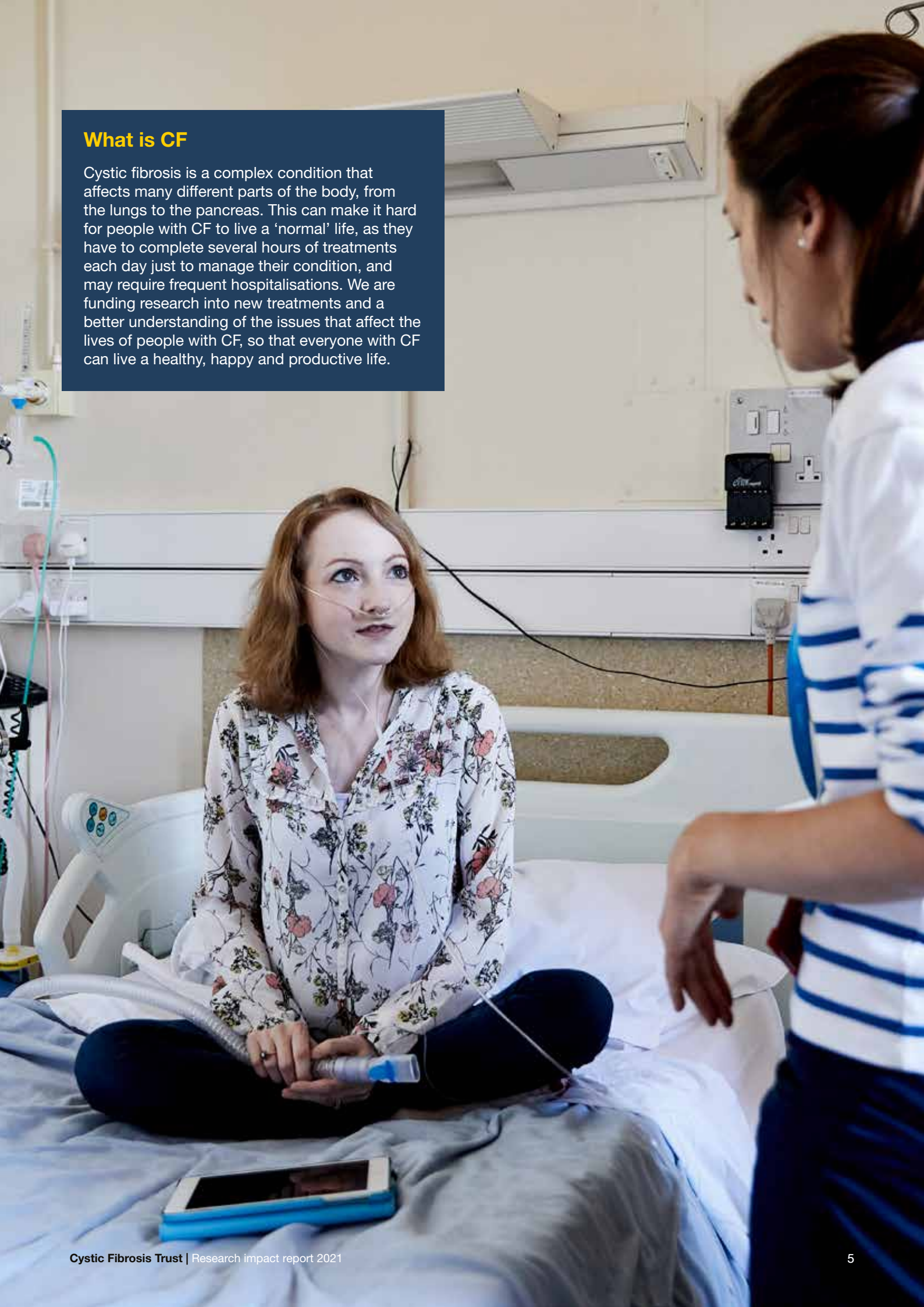
Throughout the whole cycle of research funding, we have involved the CF community: from setting our research priorities and making funding decisions, through the development of the research programme, to sharing results. This ensures we focus on funding the research that matters most to people living with cystic fibrosis. Funding and supporting research that will benefit people with CF is at the centre of everything we do, helping to ensure every person with CF to live a long and full life.

Dr Lucy Allen

[1] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390.

What is CF

Cystic fibrosis is a complex condition that affects many different parts of the body, from the lungs to the pancreas. This can make it hard for people with CF to live a 'normal' life, as they have to complete several hours of treatments each day just to manage their condition, and may require frequent hospitalisations. We are funding research into new treatments and a better understanding of the issues that affect the lives of people with CF, so that everyone with CF can live a healthy, happy and productive life.



Our current research comes under the following topics:

Tackling the underlying cause of CF

Cystic fibrosis is caused by having two mutated copies of the CF gene, known as CFTR. This leads to errors in the amount and function of the CF protein produced around the body. The most effective way of treating CF would be to restore the function of the faulty CF protein or to correct the CF gene, which could lead to people with CF living longer and healthier lives. Research is underway to treat this underlying cause of CF in a number of ways, both by directly acting on the CF gene and protein, or by working indirectly to improve other ways cells work to compensate for the lack of healthy CF protein.

Understanding and treating lung infections

Most people with CF will develop many bacterial, fungal and viral infections throughout their lifetimes. Once these infections adapt to the environment within CF lungs, they can be extremely difficult to treat. Many infections are even becoming resistant to the strongest drugs available. We are funding research into some of the most common and serious CF infections, including *P. aeruginosa* and *M. abscessus*, to detect infections sooner, develop better treatments and ultimately prevent irreversible lung damage in people with cystic fibrosis.

Understanding and treating the symptoms of CF

Cystic fibrosis affects many different parts of the body, including the lungs, liver, pancreas, gut and bones. This can lead to a range of different symptoms such as CFRD; gastrointestinal (GI) symptoms like abdominal pain, bloating and diarrhoea; and joint pain. These symptoms can significantly increase the burden of care and reduce quality of life for people living with cystic fibrosis. We are funding research into faster ways of detecting these symptoms, to achieve a greater understanding of their underlying causes and implement better ways to manage them.

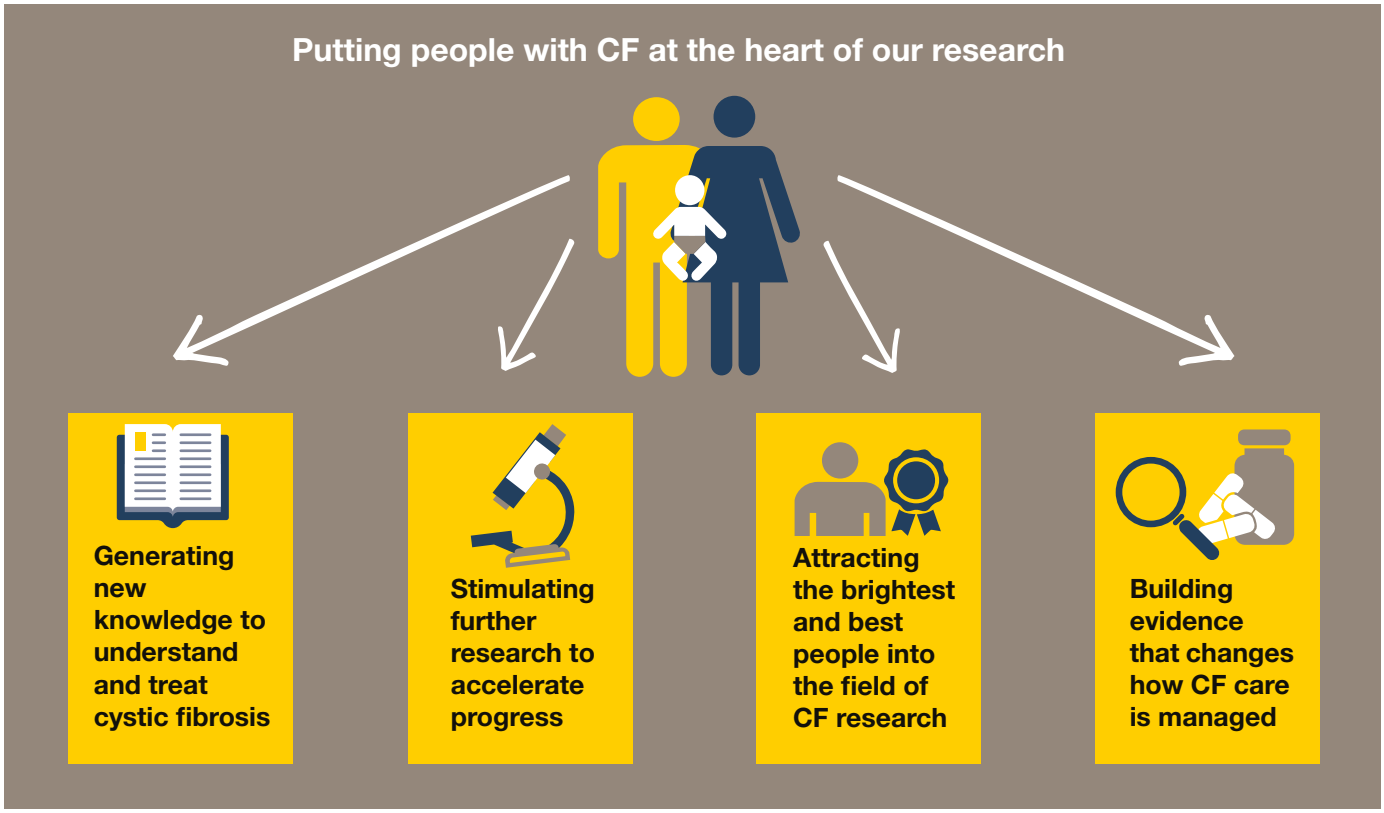
Digital health research

In the future, the way someone with CF is treated is likely to be personalised to each individual. This will encompass tailored approaches to all aspects of CF care. Our digital health research programme allows researchers to understand CF on a person-by-person basis, with an additional goal of minimising disruption to day-to-day life.

How we invest in research

The cystic fibrosis transmembrane conductance regulator (CFTR) protein has a role to play in the function of many different cells and tissues through the body. The direct and indirect consequences of a faulty CFTR protein through mutations in the CFTR gene in CF are the subject of a diverse range of biomedical and clinical research. Each research advance to understand, treat and ultimately prevent the symptoms and complications of CF represents years of investment, in terms of funding and knowledge and expertise. As a consequence, the true impact of our research can be hard to demonstrate as immediate, tangible outcomes for people with cystic fibrosis.

Within this report, we have illustrated how we invest in research into key impact areas:



Our research is managed through a range of different research programmes to achieve these impacts. These include:

- **Strategic Research Centres (SRCs):** SRCs are virtual centres of excellence that bring together researchers from within and outside the field of CF, supporting scientists and other specialists around the world to work together to address specific issues arising from cystic fibrosis. SRCs are three-to-four-year grants of up to a maximum of £750,000.

- **Venture and Innovation Awards (VIAs):** VIAs support transformational and innovative research projects by bringing leveraged funding into the field of CF from external sources.

- **Summer Studentships:** This placement scheme provides promising medical and basic science undergraduates with hands-on research experience during the academic summer vacation, with the aim of attracting the brightest and best into a career in CF research. Each placement of £1,500 provides support for the student's living expenses and a contribution to their lab costs.

- **The UK CF Innovation Hub:**
The UK CF Innovation Hub is a strategic partnership between the Trust and the University of Cambridge focusing on improving lung health. The five-year programme began in 2018, and has secured a physical presence for CF research in the new Heart and Lung Research Institute (HLRI) located adjacent to Royal Papworth Hospital. The Trust aims to raise £5 million over the next five years for the Innovation Hub, which the University of Cambridge has already committed to match pound for pound to £5 million.

- **CF Syndicate in Antimicrobial Resistance (AMR):**
The CF Syndicate in AMR is a partnership between the Trust and Medicines Discovery Catapult[2], bringing together university and hospital-based researchers, people with CF and researchers from biopharmaceutical and biotechnology companies, who are working on understanding and treating bacterial, fungal and viral infections in CF and other diseases.

[2]Medicines Discovery Catapult: https://md.catapult.org.uk/

Generating new knowledge

One of our aims in funding cystic fibrosis (CF) research is to gain a better understanding of the consequences of the faulty CFTR, both in examining how the protein works, and also to learn more about the altered environment it creates in organs and tissues within the body. Generating new knowledge in these areas can lead to more effective treatments for CF-related lung infections, CF-related complications such as CF-related diabetes (CFRD), and for everyone with cystic fibrosis.

Reports of new knowledge are published as peer-reviewed articles called research papers, which form the building blocks of scientific research. Each paper represents years of work for the researchers, from the planning and design of their studies and securing funding, to gaining a set of robust, reproducible results. The results are written up and submitted to an appropriate scientific journal for peer review by experts in the field, before being published as a research paper. These discoveries can stimulate further research, leading to changes in policy or practice and the development of new CF treatments.

Since 2013, Trust-funded researchers have published 216 scientific papers to date, with many more expected from currently-funded research. The published papers include 32 papers that further our understanding of lung infections and how to treat them, 87 addressing the underlying cause of CF, and 97 that increase our understanding and treatment of CF symptoms and complications. We highlight a few examples of research papers arising from Trust-funded projects in this chapter, demonstrating our impact in improving the lives of people with cystic fibrosis.

Understanding more about CF-related diabetes

One in three adults with CF in the UK are currently living with CFRD,[3] a distinct form of diabetes unique to people with cystic fibrosis. Having CFRD can lead to poorer lung function than other people with CF and can ultimately shorten lives. Day-to-day CFRD requires careful dietary monitoring, regular monitoring of blood sugar levels, and insulin injections multiple times a day. The CF community identified preventing the development of CFRD as a top health priority in 2017.[4]

"Having CFRD affects me as a performer. I've had to learn a lot about listening to my body and when I have to take a break! My ever-changing Levemir (insulin) intake, injections, and a Libre sensor in my arm are all things that have taken me time to come to terms with and affected me initially, as body image and insecurity is a huge thing for me. However, having a sensor on my arm is not only going to benefit me but is going to make a greater impact on how I manage my CFRD in the future – it's also what makes me, me."

Millie, musical theatre student who has CFRD

Millie

Professor James Shaw, Principal Investigator
University of Newcastle, UK

Award type: SRC

Funding: £750,000

CF topic: Understanding and treating the symptoms of CF

Although it's a well-known condition to CF clinicians, exactly how CFRD develops on a cellular level isn't yet fully understood. Addressing the CF community's prioritisation of CFRD research, in 2017 we awarded Professor James Shaw and colleagues their first £750,000 SRC grant to investigate the causes of CF-related diabetes. The funding supported eight investigators in four countries with a range of different expertise. Over the three-year SRC, they studied the role of different functions of the pancreas to understand the processes that lead to the development of CF-related diabetes.

The pancreas has two main functions: to produce digestive juices and to make hormones which regulate blood sugar. These functions take place in different cells within the pancreas. However, the precise mechanism that causes CFRD to develop and which cells in the pancreas are involved remains unknown.

Focusing on the hormone-producing part of the pancreas, the SRC team contributed important new knowledge on the sequence of events that leads to the development of CFRD. Their research papers reported on the absence of the CF protein in insulin-producing cells.[5,6] This is a very important finding because this suggests that CFTR is unlikely to play a direct role in the production of insulin.

[3]UK Cystic Fibrosis Registry, Annual Data Report 2019, Published August 2020. www.cysticfibrosis.org.uk/registry
[4]www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390.
[5]White M et al 2019, Journal of Clinical Endocrinology & Metabolism, 105(5): 1366-1374
[6]Rotti et al 2018 Journal of Pathology 188(4): 876–890

As the changes within the hormone-producing parts of the pancreas only partially explain what is happening, there must be other factors that lead to the development of CFRD. The researchers concluded that damage to the digestive-juice-producing parts of the pancreas could be contributing to the development of CFRD. (A separate symptom of CF is damage to the cells that produce digestive juices, known as pancreatic insufficiency.)[7] We have since awarded the team a second SRC grant to investigate whether signals from the damaged digestive-juice-producing part of the pancreas cause CF-related diabetes.

This Trust-funded research has led to a new direction for CFRD research. In the future this could lead to entirely new approaches to treating diabetes, avoiding the need for insulin injections and moving us a step closer to the CF community's research priority of preventing CFRD altogether.[8]

"My hope for CFRD in the future is that it doesn't bring anxiety and complication to the CF community. Maybe we will be able to come off insulin/diabetic medication altogether and that one day, people with CF won't be diagnosed with CFRD at all."

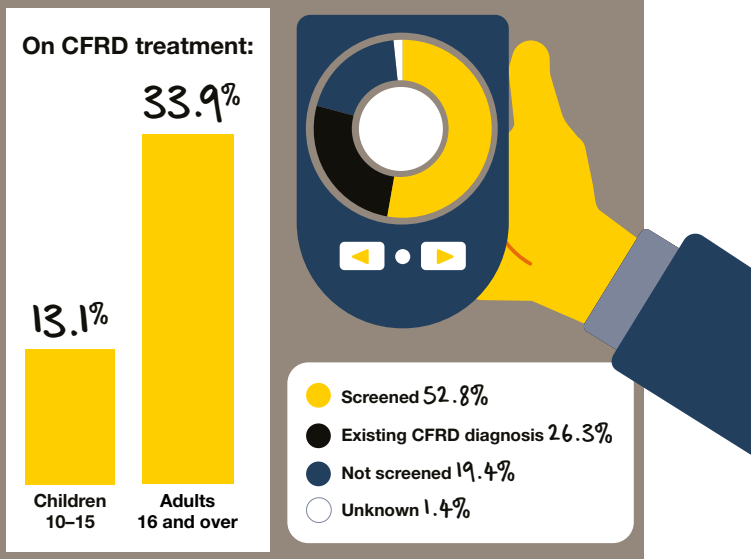
Millie, musical theatre student who has CFRD

What is CF-related diabetes?

Insulin is an important hormone that helps to regulate the amount of sugar in the blood. In CFRD, the body can't release enough insulin from where it is made in the pancreas; the body also responds differently to the insulin that is released, which means that the sugar levels in the blood aren't regulated properly. The signs and symptoms of CFRD share similarities to both Type 1 and Type 2 diabetes, but CFRD is a distinct condition, with a different underlying cause.

An early diagnosis of CFRD and insulin injection treatment can have a positive benefit for health and may protect against later diabetes-related complications, such as nerve damage.

Developing CFRD is one of the most common complications of cystic fibrosis. According to the latest UK CF Registry report, of the 7,600 people with CF who were within the age range for CFRD screening, 2,300 (of these approximately 34% were adults aged 16 and over) reported that they were receiving treatment for CF-related diabetes.



[7] www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/how-does-cystic-fibrosis-affect-the-body/symptoms-of-cystic-fibrosis/digestive-system
[8] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390.

Breaking down the resistance of *Pseudomonas aeruginosa* to treatment

P. aeruginosa is a bacterial species that causes serious infections in the CF lung. These bacteria create a protective slime known as a 'biofilm' to defend themselves from antibiotics, developing a resistance to antibiotic treatment. Research to clear *P. aeruginosa* infections is a priority for the CF community.[9] Understanding how these biofilms form could lead to the development of more effective antibiotics to treat CF-related infections.

Like humans, bacteria are also susceptible to viral infections. The viruses that infect bacteria are known as bacteriophages or 'phages'. Bacteriophages are being studied as a possible way to help treat bacterial infections. Some bacteriophages are very effective in killing bacteria but some can have a mutually beneficial relationship with bacteria, helping them survive. An example of the mutually beneficial bacteriophages are the 'Pf phages' associated with *P. aeruginosa*.

Together with the charity Action Medical Research, the Trust is funding Drs Bharat and Tarafder at the University of Oxford to study the biophysical properties of biofilm. They've recently uncovered important new evidence of how the Pf phage associated with *P. aeruginosa* helps form a physical barrier around individual bacteria within the biofilm. This physical barrier blocks antibiotics from reaching the bacteria, making the infection harder to treat.[10] Based on this evidence, they are now studying methods to break open this barrier and prevent it from forming. If researchers can design drugs to remove one of the elements of the biofilm of *P. aeruginosa*, for example, by exploiting its relationship with Pf phages, existing antibiotics may be effective again. This could mean that people with CF can clear the infection more easily and have healthier lungs as a result.

Dr Tanmay Bharat, (LEFT) Principal Investigator & Dr Abul Tarafder, (RIGHT) Co-Investigator, University of Oxford, UK

Award type: VIA

Funding: £89,917
Leverage: £89,917 from Action Medical Research

CF topic: Understanding and treating lung infections

Tanmay Bharat photo: credit: EMBL Photolab/Marietta Schupp.

"We have uncovered a new way *P. aeruginosa* bacteria, quite literally, shield themselves against antibiotics by surrounding themselves in a protective coating of rod-shaped viruses. Now that we understand this coating at the molecular level, we are designing drugs that will break it down so antibiotic treatments can be more effective."

Dr Abul Tarafder, first author of the paper, University of Oxford

"This research project was only made possible due to funding from the Cystic Fibrosis Trust and Action Medical Research, working in partnership. Our joint work increases the potential of developing treatments and we're really proud to have funded five studies together so far."

Julie Buckler, CEO of Action Medical Research

[9] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390.
[10] Tarafder *et al* 2020 Proc Natl Acad Sci U S A. 117(9):4724-4731

Developing novel techniques to test new CF drugs

Mucus forms a thin layer of liquid that traps, kills and helps sweep away debris and bugs from the surface of the lungs. However, the properties of mucus in people with CF are dramatically different compared to mucus in people without. Cystic fibrosis mucus has less water in it, making it thick and sticky; the pH (the acid/alkali balance) of the mucus is also more acidic. These differences lead to increased susceptibility to lung infections and obstruction of airways, causing damage to the lungs and making breathing harder.

Led by Dr Mike Gray, Reader in Cellular Physiology at Newcastle University, Trust-funded researchers within our 'Restoring airway function using alternative chloride channels' SRC have developed a new method for measuring mucus layer pH.[11] The new method allows pH to be measured in real time during laboratory cell culture experiments, making the studies more efficient to conduct. It can be used to test the effectiveness of potential new drugs that restore the more 'normal' properties of CF mucus, and thus improve lung health in people with cystic fibrosis.

"This new technique is relatively simple to perform; it doesn't require specialised equipment. Importantly, it has the potential to assess the effects of new therapeutics, not only for CF but also for other chronic airway diseases, such as asthma and chronic obstructive pulmonary disease."

Dr Mike Gray, SRC Principal Investigator, University of Newcastle

Dr Mike Gray, Principal Investigator
University of Newcastle, UK

Award type: SRC

Funding: £750,000

CF topic: Tackling the underlying cause of CF

Generating new knowledge in the lab about the complexities of CF is the bedrock of developing more effective and less disruptive ways to treat the condition. Research funded by the Trust has created significant advances in our understanding which, in the future, will lead to longer and healthier lives for people living with cystic fibrosis.

[11]Saint-Criq et al 2019 J Vis Exp 148 e59815, doi:10.3791/59815 ; www.jove.com/t/59815/real-time-semi-automated-fluorescent-measurement-airway-surface

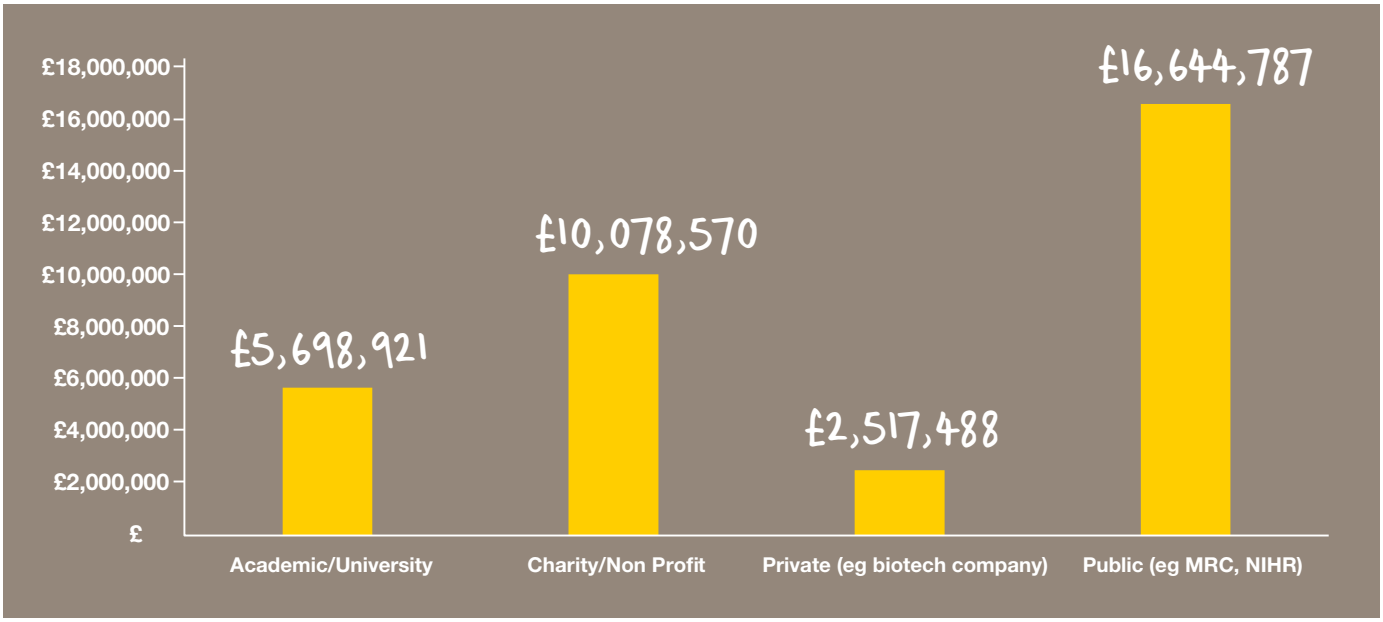
Stimulating further research

Making progress in understanding and developing new treatments for cystic fibrosis (CF) requires knowledge and insight from a wide range of specialist researchers, as well as a large amount of resource.

The Trust's research strategy facilitates a collaborative approach to investing and enabling research to use our funding to the greatest effect. We also co-fund preliminary research studies with other charities, universities and private companies. The results from these preliminary studies can be used to secure larger research grants from other funders, and facilitate conversations between diverse research groups through collaboration.

From the £18.4 million we have invested in CF research, we have leveraged an additional £34.9 million from external partners. This includes esteemed publicly-funded research organisations such as the Medical Research Council (MRC) and the National Institute for Health Research (NIHR). By stimulating further research in this way, we can achieve greater impact for people with cystic fibrosis.

Additional funding secured as a result of funding by the Trust

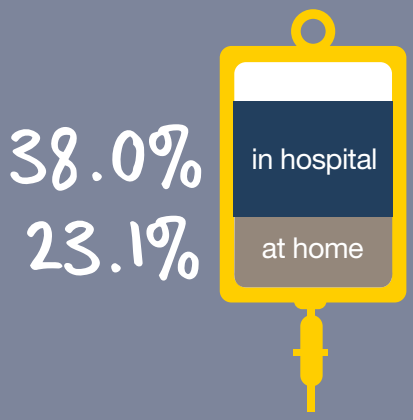


A great example of how we stimulate further research is the collaborative work we are doing to develop new antimicrobial drugs to tackle CF lung infections. Since 2013, the Trust has invested £7.6 million to understand and treat lung infections, a top research priority for people with cystic fibrosis.[12] Our multidisciplinary investments within SRCs have laid the foundations of a greater understanding of CF lung infections, particularly the aggressive infections caused by *Mycobacterium abscessus* and *Pseudomonas aeruginosa*.

To build on and further expand some of the collaborations and exciting research started within our SRC programme, and in response to health priorities identified by the CF community, we have established two pioneering new initiatives: the UK CF Innovation Hub and the CF Syndicate in Antimicrobial Resistance (AMR). These programmes aim to enhance the technical knowledge and expertise, building on new and existing collaborations between researchers and clinicians working in this area, along with leveraging additional investment to accelerate progress towards the development of new antibiotics.

44.5%

of people had at least one course of IV antibiotics in 2019.



Antimicrobial treatments have been a key factor in the massive improvements in quality and length of life in people with CF over the last few decades. However, some CF infections are becoming resistant to the antimicrobial drugs that are used to treat them (also known as antimicrobial resistance). Left untreated, these infections can cause permanent lung damage, meaning people are more breathless and have less energy to do day-to-day activities. Ultimately, a lack of effective antimicrobial drugs can shorten the lives of people with cystic fibrosis.

[12] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390

Developing personalised medicines for *P. aeruginosa* infections

There are thousands of different strains of the CF infection-causing bacteria *P. aeruginosa*, some of which respond very differently to the same antibiotics. Understanding more about the differences in these strains is an important area of research, as it could mean developing medicines that target the specific infections that a person with CF has.

However, when developing new medicines in the lab, many university and biopharmaceutical company researchers can only access reference strains of *P. aeruginosa*. The reference strains are different to the strains that people with CF are infected with and may give misleading results, as they don't fully mimic the *P. aeruginosa* strains found in cystic fibrosis.

Professor Jane Davies, Principal Investigator
Imperial College London

Award type: SRC

Funding: £750,000

CF topic: Understanding and treating lung infections

Professor Jane Davies is Professor in Paediatric Respirology & Experimental Medicine at the National Heart and Lung Institute, Imperial College London and an Honorary Consultant in Paediatric Respiratory Medicine at the Royal Brompton & Harefield NHS Foundation Trust. She is the Principal Investigator of our 'Personalised approaches to *P. aeruginosa*' SRC. One of the aims of this SRC is to better understand the adaptation and survival tactics of different strains of *P. aeruginosa* found in CF lung infections. To do this, Professor Davies has collected samples of *P. aeruginosa* from people with CF who attended her clinics, cataloguing and storing them at Imperial College.

This biorepository of clinical strains has not only provided an invaluable resource for Professor Davies' research to understand and treat *P. aeruginosa* infections, but has been shared with a wide range of new collaborators from pharmaceutical and biotech companies interested in developing new antibiotics for *P. aeruginosa*. Giving these researchers access to samples of the clinical strains of *P. aeruginosa* will make the medicines more effective than those developed using reference strains. The Trust has supported some of these new collaborations with funding from our VIA scheme.

"We collect and store bacteria once the hospital microbiology lab has completed their testing; we also collect clinical information from people with CF who consent to this. Since we started in 2014, we have collected over 9,000 samples from more than 800 CF patients at the Royal Brompton Hospital in London. Many are from the same patients, which will eventually allow us to examine how *P. aeruginosa* changes over time during a chronic infection in powerful longitudinal studies. We also have a number of academic and industrial partners, working on the development of new medicines to beat antimicrobial resistance who are benefitting from this collection, such as Cycle Pharma and Helperby Therapeutics."

Professor Jane Davies, SRC Principal Investigator, Imperial College London

Professor Davies and her colleagues have shown the value of setting up a repository of clinical strains of *P. aeruginosa* towards understanding and beating its antimicrobial resistance. This is an example of one of many banks of microbiology samples around the country. Each isolate within the repository has been carefully catalogued, which can be time consuming, and the process for sharing samples with others can be frustratingly slow. Within our CF Syndicate in AMR (outlined on page 19), we're aiming to streamline the process by establishing a National CF AMR biorepository, making it easier to share samples more broadly.

Professor Jane Davies

Designing new, cutting-edge antibiotics

We know that improving lung health could make a big difference to everyone with CF, both on a day-to-day basis and to improve quality of life. Researchers within the UK CF Innovation Hub are addressing the need for more effective antimicrobials by tackling two of the most devastating bacterial infections in the CF lung, caused by the bacteria *P. aeruginosa* and *M. abscessus* respectively. Treatment for these infections requires long courses of antibiotics with unpleasant and toxic side effects. If not treated effectively, these infections can cause life-shortening lung damage. The presence of *M. abscessus* infection can also be a particular concern during discussions about organ transplants. Better treatments and eradication of these infections was highlighted as among the top 10 health priorities by the CF community in 2017.[13]

Professor Andres Floto, Director of the UK CF Innovation Hub, University of Cambridge

Award type: UK CF Innovation Hub

Funding: £5 million
Leverage: £5 million from University of Cambridge

CF topic: Understanding and treating lung infections

Researchers within the UK CF Innovation Hub have already identified new drug targets for antibiotics against *M. abscessus* and *P. aeruginosa* using sophisticated genetic analyses. Medicinal chemists are pioneering a novel technique called 'fragment-based drug design' (FBDD) against the new *M. abscessus* drug targets. This is the first time FBDD has been used in the field of antimicrobial drug design, and has led to two publications to date.[14]

[13] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390
[14] Whitehouse et al 2019 J Med Chem, 62, 15, 7210–7232, and Thomas et al 2020 Nucleic Acids Research, Volume 48(14) 8099–8112.

Computer models of all 3,400 proteins of *M. abscessus* have also been generated and made available in a new freely-accessible database,[15] helping researchers worldwide to tackle the problem of developing antimicrobial drugs. This resource is important as we need as many potential medicines in development as possible to succeed in developing new effective antibiotics.

Following further development from the medicinal chemists, the potential new medicines will be ready to be tested in clinically relevant strains of *M. abscessus* and begin the next stage of their development into new medicines. Commenting on the progress made, a member of the International Scientific Advisory Board of the UK CF Innovation Hub said, "The antibiotic discovery work is 'the winning horse out of the stable.'"

Accelerating the development of new antimicrobial drugs

There are many stages that need to be completed before a promising drug candidate can be licensed and made available to people with cystic fibrosis. The various stages of drug development include complex lab-based studies to confirm that the potential medicine works; is likely to be safe; and is likely to get to the right part of the body when it is given to a person, and then be removed again afterwards. As no laboratory model can entirely mimic what may happen in humans, many different versions of these tests are completed to be as sure as the researchers can be that the drug will be safe and effective. The next stage is moving to clinical trials, bringing with it different challenges in terms of biostatistics, formulation, and many regulatory steps.

The CF Syndicate in AMR is a partnership between the Trust and Medicines Discovery Catapult (MDC) that was created to address challenges in CF antimicrobial discovery and development. The aim of the Syndicate is to accelerate discovery and translation of promising antimicrobial treatments to the clinic and ultimately bring better, more appropriate treatment options to people affected by cystic fibrosis. Launched in 2019, it has successfully attracted a diverse range of academic, biotech and biopharmaceutical expertise and members of the CF community to form its Steering Committee and drive this agenda. The committee is chaired by Dr Deborah O'Neil OBE, and Professor Jane Davies serves as its Vice Chair.

[15]Skwark MJ, Torres PHM, et al Database, Volume 2019, Issue 1, 2019, baz113

"The Syndicate is about making the most of investments that the Trust has already made, accessing the innovative research that is taking place in small companies and also bringing on board people with CF, to make sure that we're focusing on their needs and priorities.

"We've brought a group of people together who wouldn't normally sit around a table together, including people with CF who are part of the Steering Committee. We've identified the key obstacles holding back CF antimicrobial drug development, and we're working collaboratively on ways to overcome them to enable the development of a pipeline of new CF antimicrobial drugs."

Jessica Lee, Senior Programme Manager, Medicines Discovery Catapult

Together, the Syndicate is developing a suite of tools to accelerate the drug discovery and development pathway for industry, which include a set of Target Product Profiles (TPPs). These TPPs set out the essential requirements that new antimicrobial treatments should meet to fulfil the needs and priorities of people with CF, to guide and catalyse drug discovery in cystic fibrosis. The TPPs will be launched in Summer 2021. (More about the development of the TPPs is explained in 'Putting people with CF at the heart of our research' on page 30).

Plans are also underway to create a virtual CF AMR biorepository, linking together sites across the UK that hold vital clinical samples of microbes found in the lungs of people with CF, to facilitate simpler and easier access. This virtual biorepository will include Professor Davies' collection of *P. aeruginosa* samples at Imperial College (see 'Developing personalised medicines for *P. aeruginosa* infections' on page 16).

Jessica Lee

The journey from the lab bench to the licensing of a new medicine requires a wide range of expertise and a huge amount of investment. Funding from the Trust has had a significant impact in moving new treatments for CF lung infections through this pathway. We have stimulated lab-based research in new areas through co-funding preliminary and innovative research studies, and encouraged collaborative working to advance studies towards the clinic through our Strategic Research Centres. Together with our UK CF Innovation Hub and the CF Syndicate in AMR partnerships, these research studies and programmes hold huge promise in improving the way CF lung infections are treated in the future.

Attracting the brightest and best to CF research

Behind every step towards a new treatment or development in our understanding of cystic fibrosis (CF) is a CF clinician or researcher working hard to create change. To ensure that people with CF can lead better and longer lives in the future, we support the CF researchers of today and develop the experts of tomorrow.

We aim to attract the brightest and best early career researchers into the field of CF research, offering them training and guidance to further their careers, and gain invaluable experience to explore their own ideas and collaborate with multidisciplinary, world-class experts. These experiences shape the careers of researchers and clinicians and ultimately contribute to the advances that will create a brighter future for people living with cystic fibrosis.

We equally recognise the importance of attracting and retaining many world-leading experts to work in CF research, a field which requires constantly changing expertise to make new treatment breakthroughs. For example, the results of a study from one expert are often interpreted and added to by an expert in a very different field, some of whom may be applying their knowledge to CF research for the first time. Where this expertise is in a new, emerging area of science, we may be competing for their attention with other areas of medical research. We are proud to have funded 138 Principal Investigators across the UK and across the world.

Inspiring a career in CF research

By funding undergraduate scientists and early career researchers, we are cultivating the next generation of CF researchers, equipping them with the skills, expertise and collaborative networks to make significant contributions towards the development of new treatments for CF in the future.

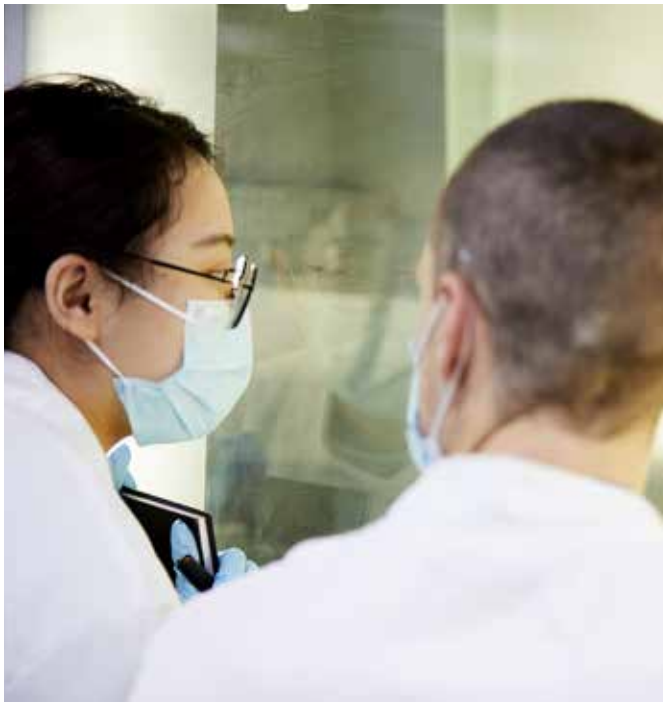
Our £1,500 Summer Studentship placements open the door into research for the next generation of CF researchers. The placements provide science, medical or pharmacy students with hands-on experience on a CF research project for six to eight weeks. Run in collaboration with Asthma UK and the British Lung Foundation Partnership, the scheme has funded 46 undergraduate placements so far. Students have told us that they provide an invaluable experience and have influenced their future career plans, giving them the potential to become the world-leading CF experts of the future.

"I really enjoyed the summer studentship. I felt like a fully-fledged scientist for two months. It pushed me to seriously consider pursuing an MRes or PhD focused on CF research in the future. My interest in research began in my BSc dissertation and the studentship gave me even more reason to work towards a career in research. I have both the Cystic Fibrosis Trust, as well as my supervisor Professor Baines, to thank for guiding me towards that decision!"

Hafssa, Summer Student in 2019

Our £750,000 Strategic Research Centre (SRC) awards provide funding to recruit students studying for a PhD, or early-stage career researchers in their first basic or clinical research position. Working as part of an internationally-collaborative team within an SRC provides these early career researchers with the opportunity to contribute to ground-breaking discoveries and further their own career in CF research. Since 2013, we've supported 89 early career researchers through the SRC programme. The multidisciplinary nature of the SRC also offers opportunities to spend time working in a different lab across the SRC, learning or passing on new techniques while also obtaining fresh perspectives on their own projects. These exchange visits and sharing of expertise can speed up progress in developing new treatments for people with cystic fibrosis.

Newcastle based PhD student Livia Delpiano (funded through our 'Restoring airway function using alternative channels' SRC[16]) was given an opportunity to spend four months in Utrecht, the Netherlands, to study organoids in the lab with the pioneer of this research, Professor Jeffrey Beekman. Organoids are grown from cells donated from people with CF and are an important technique to test whether an individual with CF is likely to respond to an existing or new CF treatment. This technology is currently being used in the ground-breaking HIT-CF clinical trial.[17] Training more CF researchers to grow organoids in the lab and gain the expertise in using them to test novel treatments will help make the CF drug discovery process faster and more efficient.



[16] www.cysticfibrosis.org.uk/the-work-we-do/research/cf-research-topics/tackling-the-underlying-cause/src-13-gray

[17] An example of where organoids are being used is the European HIT-CF research programme. In HIT-CF organoids are grown from individuals with CF, testing whether individuals with rare CF mutations are likely to respond to medicines currently in development. www.hit-cf.org

Livia Delpiano

"As well as a chance to use and learn new techniques, the visit was a great opportunity to interact with researchers with different biomedical and clinical expertise, which has helped me develop a broader perspective about my work. A year later, I'm still in touch with another Trust-funded researcher in Utrecht and we're collaborating on our research. I am very grateful to the Trust and all the supporters for this fantastic opportunity."

Livia, Trust-funded third year PhD student at Newcastle University

Becoming an independent scientist

Working in research is a competitive career path. After completing a PhD, it can be increasingly difficult to obtain further funding and secure a permanent research position. The experience of working within our SRC programme provides talented PhD researchers and those doing their first 'post-doctoral' research jobs with the skills and expertise to successfully compete with their peers to obtain funding for the next stage of their career. Ultimately, researchers must be able to demonstrate their independence to further their careers and continue to contribute to CF research.

Dr Marta Vilà González is an early career researcher working at the Stem Cell Institute, University of Cambridge. She is pioneering the use of cutting-edge induced pluripotent stem cell technology to derive ionocytes to study in the lab. Ionocytes are a new type of lung cell and were only very recently characterised. They have been shown to contain large amounts of CFTR, the protein affected in CF, and are therefore an important cell type to understand to develop effective treatments for cystic fibrosis.

Dr Vilà González began working in CF research for the Trust's UK CF Innovation Hub in 2018, funded directly as a post-doctoral research assistant. In 2020, she was awarded a prestigious Sir Henry Wellcome Postdoctoral Fellowship, giving her financial independence to continue her CF research. The award recognises her potential as a future leader in this field, and gives her the opportunity to further her career in CF research.

Dr Marta Vilà González

"Receiving the Sir Henry Wellcome Fellowship was a very important milestone in my career. It has been a great opportunity for me to broaden my knowledge and make my research more multidisciplinary by establishing exciting collaborations that will be maintained through my scientific career. Ultimately, obtaining this award is a key step to become an independent scientist and will help me establish myself in the field of CF research. I'm grateful for the funding from the Cystic Fibrosis Trust for starting me out on this path."

Dr Marta Vilà González, Sir Henry Wellcome Fellow, Cambridge University

Supporting clinical researchers

Clinical research scientists provide an important link in helping to move lab-based CF discoveries towards clinical trials. They have a different perspective to their lab-based colleagues and can help recruit people with CF to participate in research. However, for many clinical researchers, it can be extremely difficult to balance the demands of maintaining their clinical work and obtaining funding for 'dedicated' time to conduct CF research. As a consequence, clinical research is a career path that few clinicians choose to pursue.

When the Trust awarded a £750,000 SRC grant to Dr Mike Gray in 2013, it meant that the Newcastle University-based researcher could use his allocation of the multi-centre budget to secure additional funding from the university. This provided the initial funding for clinician Dr Iram Haq to undertake research supervised by Dr Malcolm Brodlie, Dr Mike Gray and Professor Chris Ward. She was subsequently awarded a prestigious Wellcome Trust clinical fellowship, allowing her to carry out her PhD studying the physiology of lung epithelial cells, providing a greater understanding of these cells in health and in the paediatric CF lung. Dr Haq is now an Academic Clinical Lecturer at Newcastle University and the Great North Children's Hospital.

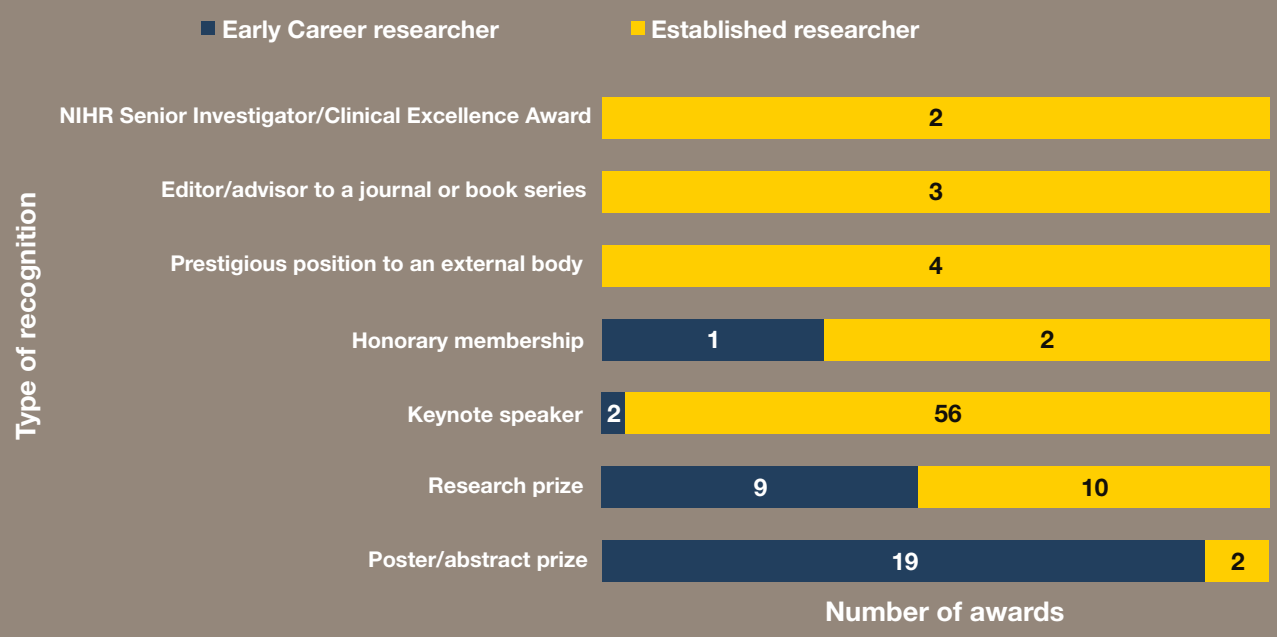
Dr Iram Haq

"After completing my PhD, I was appointed as an NIHR Academic Clinical Lecturer in April 2019. This position, supervised by Dr Malcolm Brodlie, has enabled me to continue my research alongside my clinical training in Paediatric Respiratory Medicine. I have also recently been awarded funding from the Academy of Medical Sciences, to carry out my research around the importance of specific ion channels in regulating the airway surface in diseases such as cystic fibrosis. Furthermore, I've had the opportunity to collaborate with other international CF researchers[18] and have accepted important opportunities to contribute towards knowledge and expertise within this field. This has included a recent international study funded by a Trust Summer Studentship investigating the impact of coronavirus (COVID-19) in children with cystic fibrosis."[19]

Dr Iram Haq, NIHR Academic Clinical Research Lecturer, Newcastle University

[18] https://doi.org/10.1152/ajplung.00137.2020
[19] Bain *et al* Journal of Cystic Fibrosis 2021, **20**, 25-30

How the knowledge and expertise of Trust-funded scientists and clinicians has been recognised



Working with recognised researchers

Being recognised for their contribution to CF research helps to raise a researcher's profile and establish their knowledge and expertise among their peers. This can also help make networking and sharing results easier, which is an important way for CF researchers to make progress in understanding CF and developing new ways to treat it. Since 2013, researchers we fund have received 110 research awards or other types of recognition for contribution in their field. These awards demonstrate how the Trust is supporting some of the brightest and best researchers working in CF research.

The way that excellence is recognised is different during the stages of a researcher's career. As illustrated in the chart above, at an early stage in their careers, scientists and clinicians working in CF have been more frequently recognised through prizes for conference presentations. As their career progresses, their knowledge and expertise may be honoured through invitations to give talks at conferences or to join prestigious organisations in their field.

The Trust's support for scientists and clinicians throughout their CF research career goes a long way in terms of our impact for people with cystic fibrosis. Our multidisciplinary programmes and world-class networks provide CF researchers with one-of-a-kind opportunities to develop vital skills, experience and knowledge. As a result they are helping to tackle some of the greatest challenges in cystic fibrosis.

Building evidence that changes how CF is managed

We fund research to make a difference to people living with cystic fibrosis (CF), both now and in the future. The aim of our research is to lead to future treatments and hopefully a cure for CF, as well as research that, if successful, will have a more immediate impact on the lives of people with cystic fibrosis.

When changes are made to CF care, it is important to evaluate the effects that these changes have had on people's health, to provide evidence of their impact to healthcare providers and commissioners, and to give clinicians and people with CF confidence in the way CF is managed. Two significant changes to CF care that were introduced in the last 15 years were the introduction of newborn screening (NBS) and a re-evaluation of how FEV_1 (a measure of lung function) is calculated. Trust-funded research using data from the UK CF Registry has shown that these changes have improved care of people with CF for the better – but also highlights there is more to be done. Within the Trust's digital health research programme, we are exploring ways to use healthcare data in a different way.

Investigating the impact of newborn screening

Newborn screening for CF as part of the heel-prick test became available across the UK in 2007, and is an important way for children with CF to be diagnosed as early as possible. It aims to ensure that parents and children have access to the necessary healthcare from birth, which could lead to better long-term health. Dr Daniela Schlüter's Trust-funded research within our CF-EpiNet SRC programme investigated the overall impact of NBS for CF using data from the UK CF Registry.[20] Specifically, she studied whether an earlier diagnosis reduced the differences in health in people with CF from different socioeconomic backgrounds.

Dr Daniela Schlüter , Early Career Researcher
University of Liverpool

Award type: SRC

Funding: £747,259

CF topic: Understanding and treating the symptoms of CF

In research published in 2019,[21] Dr Schlüter showed that all children with CF diagnosed through NBS had better early weight and lung function and a delayed onset of *Pseudomonas aeruginosa* lung infection, in comparison to the health of children who were diagnosed later clinically. However, within the limits of their analysis, they found that children with CF from more affluent backgrounds still do better than those from disadvantaged backgrounds.

After hearing a presentation of these findings from Dr Schlüter, Professor Kevin Southern and his colleagues in the CF service at Liverpool's Alder Hey Children's Hospital considered what changes they could make to address this.

"There are simple measures that all CF teams can take to support families from less well-resourced backgrounds. For us, this has involved exploring in a sensitive manner the barriers to attending clinic, such as transport and cost. In addition, we have increased the support we can offer with home visits from all members of the team."

Professor Kevin Southern, Director of the Cheshire, Merseyside and North Wales Network of Paediatric Cystic Fibrosis Care, Alder Hey Children's Hospital Liverpool

[20]UK CF Registry www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry
[21]Schlüter DK, Southern KW, Dryden C, *et al*. Thorax 2020; 75:123–131

Accurately assessing lung function over time

For many years, researchers and clinicians saw a sudden decline in lung health in teenagers with CF as they transitioned from paediatric CF care to an adult CF service. Young people with seemingly good lung function often found themselves being informed around the age of 18 that their lung function was significantly worse than they had been led to believe. Research funded by the Trust found that young people's lung health was being over-estimated, and that there is a trend of a gradual decline in teenagers' lung function over time, rather than a sudden decline as they become adults.[22]

When researchers and clinicians measure lung function in children with CF, it is important that they know whether any changes they see are due to CF, or to normal body changes as children grow up. Normal body changes are taken into account by applying a set of equations to the FEV_1 readings. However, until recently, researchers and clinicians around the world were using different equations, making it difficult to compare lung function in different places and, importantly, between children and adults. One equation was used to 'normalise' lung function in children and a different equation was used for adults.

Following the introduction of a new standard set of equations known as the Global Lung Function Initiative (GLI) in 2012, Trust-funded researchers investigated the impact of the new equations on CF care using data from the UK CF Registry.[23] They found that the new equations gave a more accurate prediction of lung health for both children and adults.

Dr Gwyneth Davies, Senior Investigator
UCL Great Ormond Street, Institute of Child Health

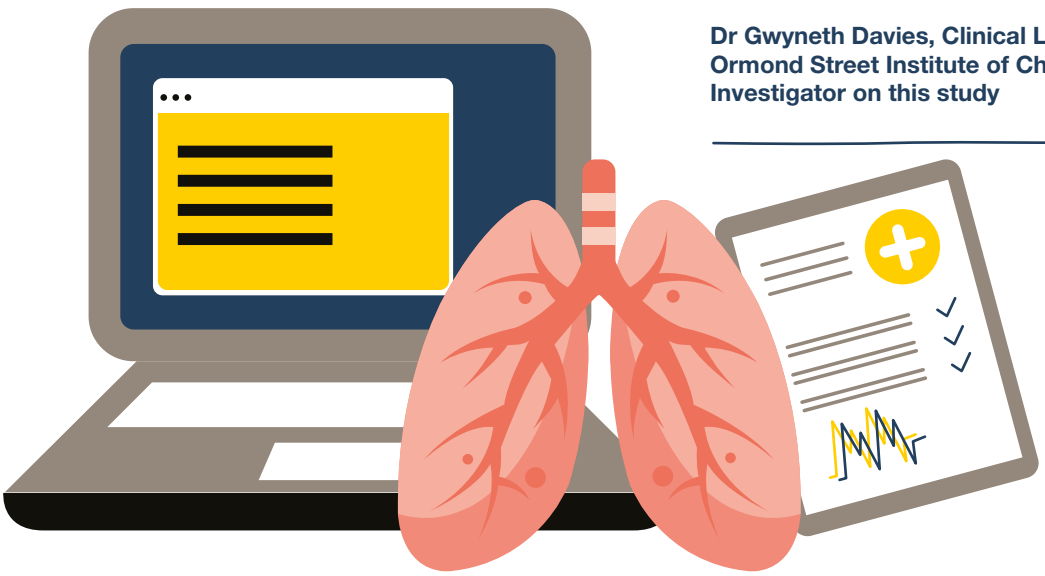
Award type: VIA

Funding: £30,150
Leverage: Institute of Child Health, in kind

CF topic: Understanding and treating the symptoms of CF

"Before the GLI equations were implemented, different equations were used for children and adults. Teenagers were falsely reassured that their lung function was normal but when they turned 18 and their lung function was calculated using the 'adult' spirometry reference equations, their lung function was a lot lower. This caused understandable distress. Now GLI equations are used the accuracy of lung function measurements is greatly improved, and there is no nasty shock for teenagers with CF and their parents."

Dr Gwyneth Davies, Clinical Lecturer at UCL Great Ormond Street Institute of Child Health and Senior Investigator on this study



[22]Stanojevic et al Eur Respir J. 2015 Jul;46(1):262-4
[23]UK CF Registry www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry

Accelerating digital health research in the coronavirus (COVID-19) pandemic

Digital health approaches to improving CF care could result in a longer, healthier life that is less burdened by their condition, addressing a top health priority identified by the CF community.[24] In practical terms, this may mean less unnecessary face-to-face clinic appointments, as well as faster diagnosis and more effective treatments when health problems develop.

Research is required to test the feasibility, accuracy and safety of using home monitoring to assess the health of people with CF, and to analyse the health data generated from the monitoring to inform improvements in diagnosing and treating lung infections. Since 2016, the Trust's digital health research programme has been exploring how home ('remote') monitoring and data generated from monitoring can be applied to make improvements in CF care.

Kirsty Hill, Co-investigator
Cambridge, UK

Award type: Digital Health Programme grant

Funding: £2.5 million grant from Cystic Fibrosis Foundation to the Cystic Fibrosis Trust

CF topic: Digital health research

Project Breathe is a current research study within the Trust's digital health research programme. Initially funded through a Venture and Innovation Award (VIA) grant, Project Breathe is now supported by a £2.5 million grant to the Trust from the US-based CF Foundation.[25] A core part of Project Breathe is the development of a smartphone app that collects data that is relevant to the health of a person with cystic fibrosis. The data can be entered into the app in a range of ways: manually, via Bluetooth, or via systems such as Fitbit. Within the research, study participants then share their data with clinicians where it can be reviewed during remote clinical appointments and may also be used to determine whether a face-to-face clinic appointment is required.

"Remote clinic saves me having to go to the hospital at a certain time and saves me time when I'm there. If I go to clinic there's a chance of picking up an infection, whereas I can't catch anything over the phone! Being able to monitor myself at home helps me feel in control of what's going on with my cystic fibrosis."

Mark, who is a participant of the Project Breathe research study

In April 2020, as the gravity of the COVID-19 pandemic emerged, the Project Breathe team made the app publicly available to allow anyone with CF to monitor their health remotely. Since then, the app has been downloaded more than 1,000 times.

[24] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390
[25] www.cysticfibrosis.org.uk/news/new-grant-to-test-how-technology-could-change-cf-care

Understanding the transmission of *Mycobacterium abscessus* lung infection

A concern about going to clinic appointments is the risk of picking up infections from other people with CF attending the same clinic, known as cross-infection. Hospitals and researchers are constantly vigilant to minimise the risk of cross-infection and act quickly when new lab-based evidence highlights the need for changes to cleaning and cross-infection practices, as shown by the discovery in 2016 that *M. abscessus* can be passed on from person to person.

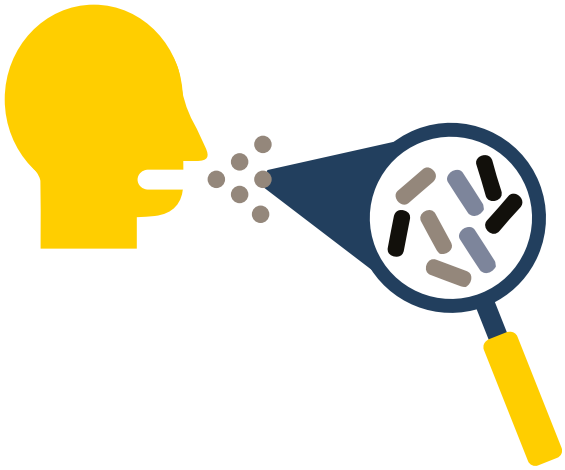
Professor Andres Floto, Principal Investigator
University of Cambridge

Award type: SRC

Funding: £745,708

CF topic: Understanding and treating lung infections

As well as diagnosing the presence of a CF infection and effective ways to treat it, it is also important to understand the source of the infection. The source of infection can change over time, as bacteria are constantly evolving to survive in different places. This information can help reduce the number of infections people develop and can also lead to changes in how CF clinical services are managed.



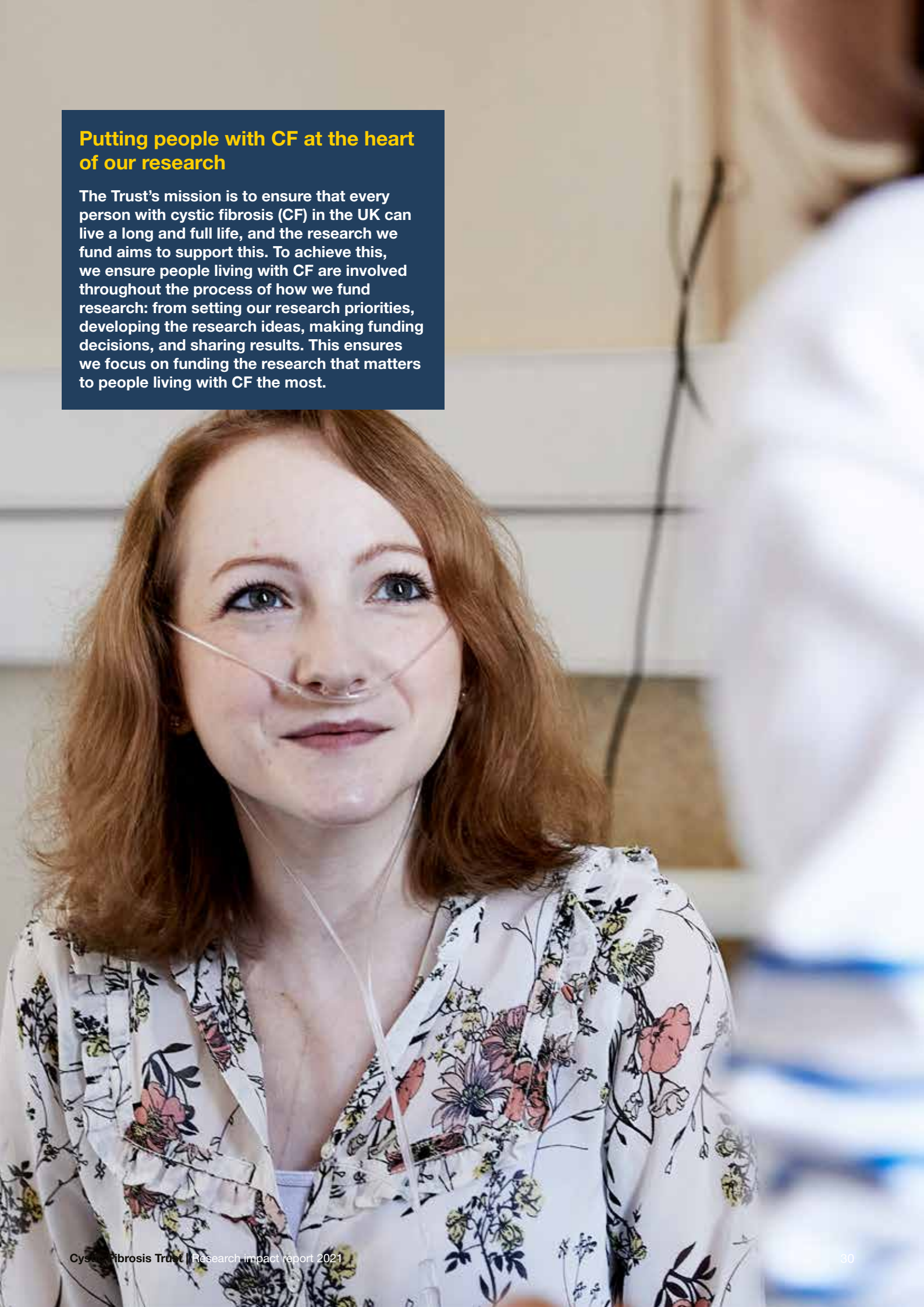
It was originally thought that people developed *M. abscessus* from environmental sources. However, in 2016, Trust-funded research led by Professor Andres Floto, Professor of Respiratory Biology at the University of Cambridge and Honorary Consultant at Royal Papworth Hospital, showed for the first time that *M. abscessus* can be passed from person to person. This important discovery, published in the prestigious journal 'Science',[26] has led to the introduction of a number of new measures to prevent people with CF from developing *M. abscessus,* improving their lung health as a result. These include the development of new cross-infection guidelines,[27] detailing rigorous and specific cleaning and segregation procedures in CF clinics to avoid infection being passed from one person with CF to another. Good air flow and increased air changes within air conditioning were also recommended, which was included as part of the 2019 design at Royal Papworth Hospital.

"It was a huge amount of work from a large, multidisciplinary team to generate the evidence that *M. abscessus* is transmitted from person to person, but it was a game changer for the way that we manage our clinics. *M. abscessus* is a devastating infection for people with CF, and we have to do anything we can to stop more people from contracting it."

Professor Andres Floto, SRC Principal Investigator, University of Cambridge

It can take many years for the impact of biomedical research to be seen in the clinic but when the impact is realised, it can be dramatic. The results of biomedical lab-based research funded by the Trust about the transmission of *M. abscessus* led to significant and long-lasting changes to CF care. Trust-funded research using data from the UK CF Registry has also demonstrated the positive impact of new ways of managing cystic fibrosis. Whatever the change may be, it is always important that there is evidence demonstrating the benefits for people with CF and their families.

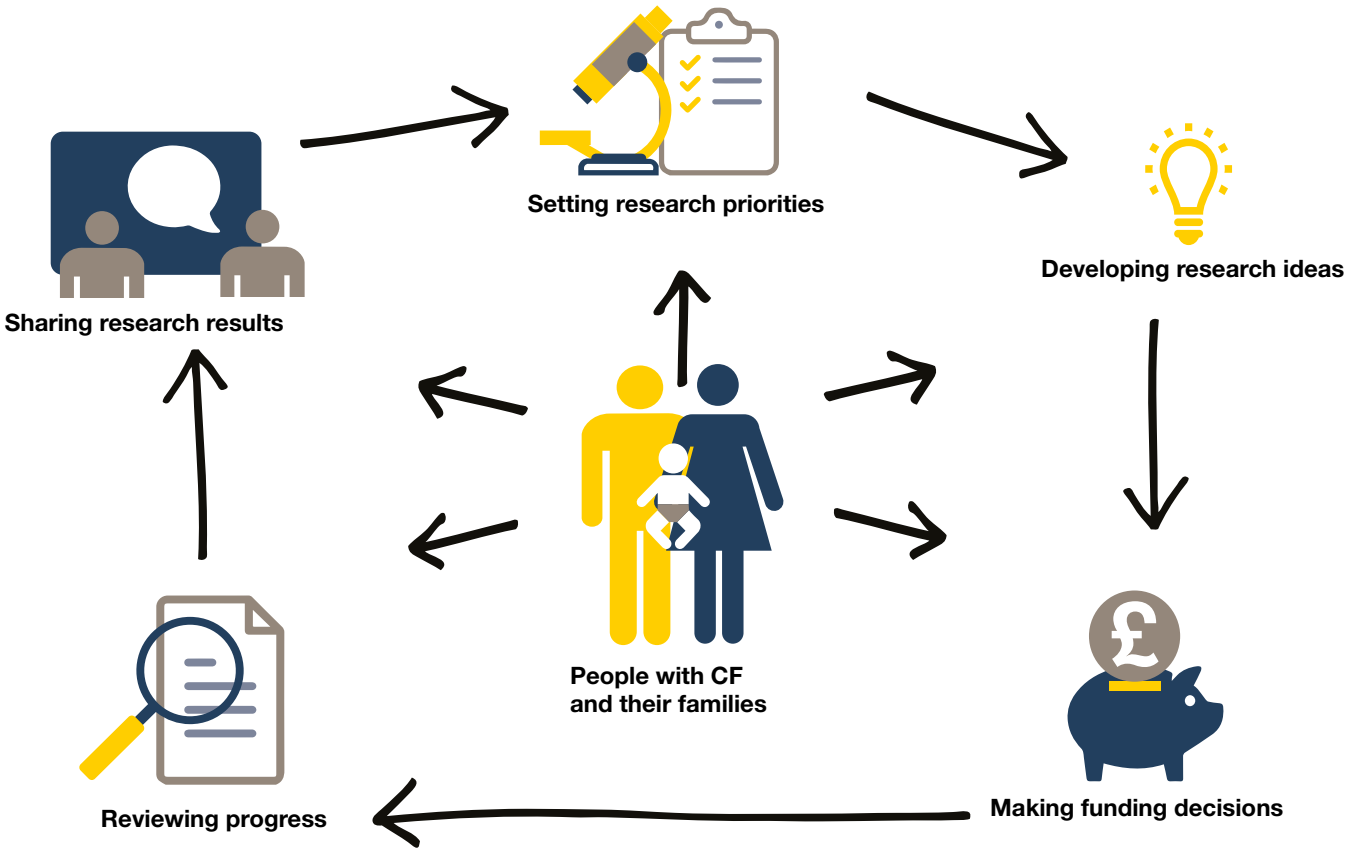
[26]Bryant et al 2016 Science 354(6313): 751–757
[27]www.cysticfibrosis.org.uk/sites/default/files/2020-12/NTM%20guidelines%20Mar%202018.pdf.



Putting people with CF at the heart of our research

The Trust's mission is to ensure that every person with cystic fibrosis (CF) in the UK can live a long and full life, and the research we fund aims to support this. To achieve this, we ensure people living with CF are involved throughout the process of how we fund research: from setting our research priorities, developing the research ideas, making funding decisions, and sharing results. This ensures we focus on funding the research that matters to people living with CF the most.

Below are examples of how we keep the CF community at the heart of the research we fund:



Setting the Trust's research priorities

In January 2017 a list of the CF community's top 10 health priorities was published,[28] identified through a project led by Professor Alan Smyth at the University of Nottingham and facilitated by the James Lind Alliance. The Trust supported the project through a Venture and Innovation Award (VIA) grant of £15,000, with matched funding from the University of Nottingham.

The priorities identified included reducing the burden of care, effective treatment in early life, tackling lung infections, and relief for gastrointestinal (GI) symptoms. The priorities have become guiding principles for our research strategy, and all applications for research funding are reviewed against them. It prompted us to specifically fund a Strategic Research Centre (SRC) grant on developing more effective treatments for the GI symptom Distal Intestinal Obstructive Syndrome (DIOS) and has informed CF researchers and clinicians in research studies funded by other sources.

The working group of researchers, clinicians and the CF community formed to identify the health priorities in the initial James Lind Alliance Priority Setting Partnership project has continued to influence and shape the CF research agenda. The recently-announced CF STORM study[29], investigating the feasibility of reducing the burden of care in people with CF taking Kaftrio, was also informed by these health priorities.

A great deal has changed for the CF community in the last few years, including the impact of CFTR modulators such as Kaftrio, any lasting effects of the coronavirus (COVID-19) pandemic, and subsequent changes in CF care and clinical trials. This year we will be engaging the CF community, researchers and clinicians to determine whether and how their research needs and priorities have changed, and how these are reflected in the Trust's future research priorities.

[28] www.cysticfibrosis.org.uk/news/your-research-priorities-revealed & Rowbotham NJ et al 2018, Thorax, 73, 388-390
[29] CF STORM is a ground-breaking trial to find out if people receiving Kaftrio can safely start to reduce the number of treatments they have to manage as part of their daily healthcare routine.

Working with people with CF to develop 'ideal drug checklists'

During drug development, researchers use a tool called a 'Target Product Profile' (TPP), which provides a checklist for the requirements a new medicine needs to meet. These include the dosing frequency and duration, the delivery method, the storage, or tolerable side effects. Where a new medicine or diagnostic tool is being developed, a common first step is to then build consensus for a Target Product Profile. For example, TPPs were developed for COVID-19 diagnostic tests and vaccines.

The Steering Committee of the CF Syndicate in antimicrobial resistance (AMR),[30] which includes two people with CF, identified that the development of a suite of TPPs could help accelerate drug development in this area. It was agreed that an innovative approach should be taken; rather than focusing a TPP around a specific medicine or test, the CF TPPs should be built around the needs and priorities of people with CF, reinforced with clinical and industry expertise. By doing this, the needs of people with CF will be at the heart of the drug discovery and development process.

To open the discussion on TPPs for new antimicrobial medicines for CF, the Syndicate Project Management team worked with members of the CF community to understand what they would like to see from new medicines to treat their infections (for example, how long treatment courses should last, how medicines should be taken, and how they'd like to see clinical trials run). In an online focus group, a group of people with CF and parents of children with CF discussed what an ideal antimicrobial drug should look like.

"The session was lively, engaging and thought-provoking. The discussion covered a range of agenda items but very much felt like an informal chat rather than a meeting. All participants were offered the opportunity to contribute as much or as little as they felt comfortable with.

"I also found listening to other CF patients and hearing about their experiences fascinating. In these modern times, when the risk of cross-infection rules out face-to-face contact between people with CF, it was so nice to feel part of a community, rather than simply isolated in our own experience of cystic fibrosis."

Luke, focus group member who has CF

An online consultation of the CF community, clinicians and representatives from the life-sciences industry was recently completed to gain further input and to help shape the TPPs. The insights from the consultation will be discussed at a Virtual Symposium, which will bring together people with CF and international leaders in CF infection drug discovery. Following the Symposium, the TPPs will be published and disseminated widely to spark drug discovery efforts and ensure that new medicines that meet the needs of people with CF will reach the clinic, faster.

[30] https://md.catapult.org.uk/syndicates/cystic-fibrosis-syndicate-in-antimicrobial-resistance and for more detail on the Syndicate see also 'Stimulating further research' section earlier in this report.

Making research funding decisions

Before we decide to fund a research project, we examine the research proposal carefully and ask a range of experts to help us ensure that the research we fund has the best chance of delivering the stated aims, objectives and impact. People living with CF, either themselves or in a supporting role such as a parent, are considered experts by experience and, together with CF research and clinical experts, form our Research Grant Review Committee. In addition, we call upon researchers and clinicians around the world to provide their views in a process called 'peer review'.

Our Research Grants Review Committee share their time and expertise with us as we assess the funding applications and assimilate the comments generated from the peer review process. Members of the Committee give their time voluntarily, and it is a time-consuming year-round commitment. We have three members of the Committee from the CF community, currently two people with CF and one parent of children with cystic fibrosis.

"The experience of having and living with CF is very different from what it is to have clinical or research expertise. As a person with CF on the Committee, my role is to add the real-life experience; it particularly helps with understanding the value and impact that research may bring to people with cystic fibrosis."

Aoife, a member of the Research Grants Review Committee who has CF

At the beginning of the annual SRC competition process, members of the Committee help us review preliminary proposals in a triage. We only request full SRC applications from proposals that members of the Committee feel meet our criteria for funding. The Research Grants Review Committee meets every spring (in person or online) to discuss the full SRC applications together with reports from at least three peer reviewers per application.

"At the meeting we discuss the merits and gaps of each application with great rigour. It's quite an open and safe environment, and the researchers are also aware that their work has to be understood by the CF community. Everyone is extremely passionate and recognises the importance of which SRCs are funded. This means there are often disagreements and going back over aspects of an application in depth to really assess the detail. What has struck me is how much everyone really cares about people with CF and really wants to fund the best research,"[31]

Aoife

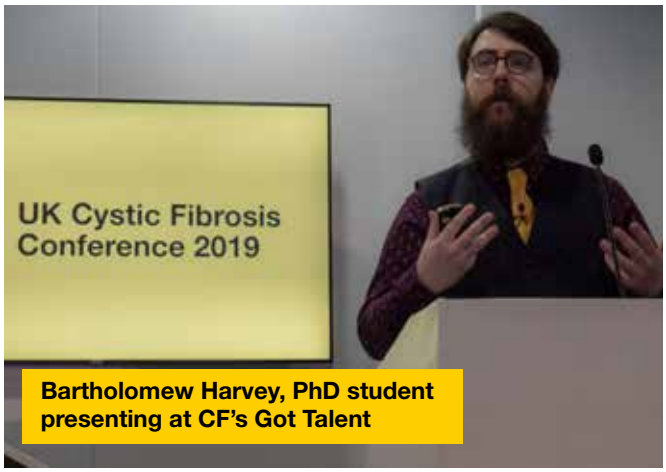
At the end of the meeting, the Committee agrees a list of SRC applications that they have ranked and will recommend for funding. The Trust's decision on which research projects to fund, based on the ranking, is centred around the budget that has been allocated for research funding and the recommendations from the Committee.

[31]You can read more detail about Grant Review Committee's role in our decision making process in an interview with Aoife on our website: www.cysticfibrosis.org.uk/news/how-do-we-decide-what-research-to-fund

Sharing research with the CF community

In our research strategy we committed to sharing more results from Trust-funded research studies with the CF community, to illustrate the extent of research underway to improve the lives of people living with cystic fibrosis.

One response to this was developing 'CF's Got Talent': a science communication competition for early career researchers to present their work to the CF community. Every year, five early career researchers working within our SRC programme are selected to give a 10-minute, non-technical presentation at the Trust's UK CF Conference (UKCFC). Since it started in 2016, we have invited 22 people from the CF community to shortlist competition finalists, some of whom have subsequently worked with the finalists to develop their presentations. The CF community watching online then votes for the winner live.



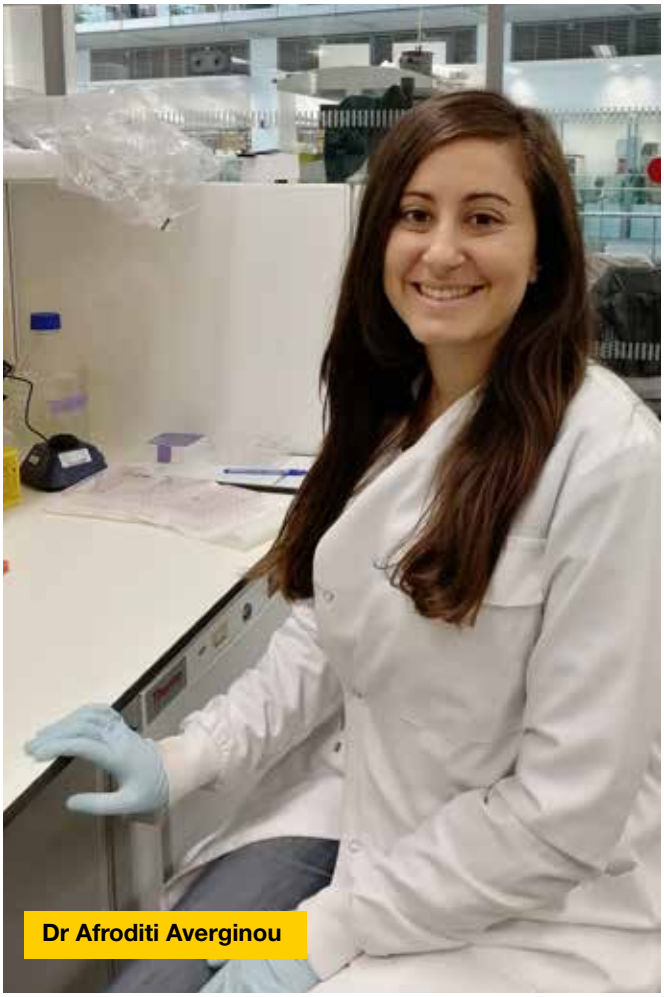
Bartholomew Harvey, PhD student presenting at CF's Got Talent

"I really enjoyed taking part in CF's Got Talent – it gave me a new understanding of cystic fibrosis. If my children are taking medication, I want to be able to understand how it works. A better understanding can lead to an appreciation of how CF affects so many body functions, and the challenges faced when trying to develop medication."

Jenny, a member of the judging panel, whose daughter has CF

"The whole experience of taking part in CF's Got Talent was very rewarding. Working in the lab, it is easy to get lost in the experiments and science, forgetting the reason why you are doing them. Being able to connect with the people that benefit from your research is inspiring and helps you refocus when things get difficult."

Dr Afroditi Averginou, winner of the competition in 2018



Dr Afroditi Averginou

Throughout this report we've highlighted the impact of our research on people with cystic fibrosis. In this section, we've highlighted where they have been directly involved in shaping this research – from what to fund and how the research is conducted, to how to improve the sharing and explanation of the results.

Thank you

We would like to thank all of the trusts and organisations that support our ground-breaking research, some of whom are mentioned on this page. Collaborating globally is vital to ensure we are providing the best possible support to the CF community.

We engage internationally in a number of ways and would also particularly like to acknowledge partnership funding from the Cystic Fibrosis Foundation (CFF), University of Cambridge, Medicines Discovery Catapult, Action Medical Research and the Asthma UK and British Lung Foundation Partnership.

Very special thanks to Dr Janet Allen FRSE, who developed and led the implementation of our Research Strategy from 2012 to 2020.

Data for this report were taken from grantee progress reports submitted to the Trust and from data submitted via the research impact database Researchfish[32]. Many thanks to our grantees for their co-operation in sharing these data with us.

Special thanks

An extra special thank you to our incredible fundraisers, challenge and event participants, volunteers and donors, including our branches and fundraising committees who are so very generous with their time and support. The money you raise can help us to create a brighter future for everyone affected by cystic fibrosis.

Trusts, Foundations and Companies

- Robert Luff Foundation
- AJN Steelstock
- Vertex Pharmaceuticals
- Garfield Weston Foundation
- Masonic Charitable Foundation
- Rosetrees Trust

Families

- The Castella Family
- The Dujardin Family

Gifts in Wills

- Brian and Roberta Balmer
- Mr James Morris McKinley

[32] https://researchfish.com/researchfish/

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